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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,151	HAMADA, HIROFUMI	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *19-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment was received and entered on 9/24/03. Applicant's election without traverse of group 1, claims 4-20, antitumor agents, and the species of *Adenoviridae* is acknowledged.

Claims 19 and 20, drawn to diagnostic agents, are withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-26 remain pending in the Application. Claim 1-18 are under consideration in this Office Action.

Applicant is reminded that claims 1-3 link inventions 1-4, and that claim 5 links inventions 1-4 to the extent that it depends from claims 1, 2, or 3. The restriction requirement among the linked inventions is subject to the non-allowance of the linking claims. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Priority

This Application was filed under 35 USC 371 and claims priority to PCT/JP00/01069 filed 2/24/00, and to Japanese Application 11/93263, filed 2/24/99. It is noted that no translation of the foreign priority document (Japanese Application 11/93263) has been received. Should the claims be rejected over art published after the foreign priority document but before the PCT publication, Applicant will not be able to rely upon the foreign priority papers to overcome this rejection until a translation of said papers has been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). This application clearly fails to comply with the requirements of 37 C.F.R.1.821-1.825. Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **The specification at pages 22 discloses an amino acid sequence in excess of 3 amino acids that is not accompanied by a SEQ ID NO. At page 27 the specification discloses a nucleotide sequence in excess of 9 bases that is not**

accompanied by a SEQ ID NO. If these sequences are listed in the current Sequence Listing, then the specification should be amended to include the appropriate SEQ ID NO in each of the passages referred to above. If these sequences are not in the current Sequence Listing, then Applicant must provide:

A substitute computer readable form (CRF) copy of the "Sequence Listing".

A substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is indefinite because none of the members of the recited Markush group is a virus, as required by the preamble. Instead the members of the Markush group are families of viruses. One cannot select a virus from a group that consists only of virus families, one can only select a virus family from such a group. This rejection could be overcome by amending the claim to require that the "virus is a member of a virus family selected from the group consisting of" etc.

Claim 15 is indefinite because it recites "the gene" without proper antecedent basis.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for virus vectors comprising a virus structural protein fused with a ligand that specifically binds to a melanocyte stimulating hormone receptor wherein the structural protein is incorporated into the outer surface of the virus, does not reasonably provide enablement for such viruses wherein the virus structural protein is not exposed on the outer surface of the virus. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed invention is a virus vector comprising a virus structural protein fused with a ligand that specifically binds to a melanocyte stimulating hormone receptor. The specification teaches that the claimed viruses should infect cells via the modified structural protein binding to the melanocyte stimulating hormone receptor. Claims 5-18 require that the virus structural protein "constructs the outer surface of the virus." If claims 5-18 further limit claim 1, then it follows that claims 1-4 embrace viruses in which the structural protein is not part of the outer surface of the virus. For example, retroviruses comprise capsid proteins that are required for the structure of the virus, but which are not exposed on the surface of the virus. The rejected claims embrace versions of retroviruses in which the capsid protein comprises a ligand that specifically binds to a melanocyte stimulating hormone receptor. However, the portions of viruses required for recognition of cellular receptors are generally arrayed on the surface of the viral particle such that they can readily interact with the receptors. See e.g. Fields (In Fundamental Virology, Second Edition, Raven Press New York, 1990, Fig. 2 at page 649). Clearly a structural protein comprising a ligand that specifically binds a receptor, but that is not on the outer surface of the virus, cannot function as intended by the specification to permit binding of the targeted receptor. The specification provides no guidance as to how to make a virus such that internal structural proteins can be used to provide target binding functions, and because such guidance is also absent from the

prior art, one of skill in the art could not use make or use such viruses without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 5-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Spooner et al (WO 94/10323, published 5/11/94).

Spooner teaches adenoviral vectors comprising an MSH alpha targeting ligand inserted as a fusion protein into the adenoviral fiber protein. See abstract; page 4, lines 24-27; page 6, lines 10-15; page 9, lines 11 and 12; page 10, lines 13-15; page 32, lines 1 and 2, and claims 3, 9-11, 2, and 23. The fusions may comprise a peptide linker, see e.g. page 5, lines 9 and 10 and page 38 lines 5-11. Pertinent to claim 8, Spooner exemplifies Ad5, which is a human adenovirus. Pertinent to claims 9-14, the viral vector may comprise a gene encoding a molecule having direct or indirect cytotoxic function such as ricin, TNF, cytosine deaminase or herpes simplex virus thymidine kinase, or encoding a tumor suppressor or cell cycle/cell death regulator such as p53, Rb, src, or bcl. See page 16, lines 7-27, and page 20, lines 27 and 28. Regarding claim 15, Spooner teaches viruses comprising an E1A gene, and/or fragments of an E1B gene. See page 14, lines 20-25. Although these genes are not exogenous to the virus, they

are considered to meet the limitations of claim 15 because they are structurally indistinguishable from exogenous versions of the same genes that would be inserted into a virus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel et al (US Patent 6,312,699, issued 11/6/01) in view of Spooner et al (WO 94/10323, published 5/11/94) and Wickham et al (J. Virol. 71(11): 8221-8229, 1997).

Curiel teaches human adenoviral vectors in which the fiber protein has been modified by attachment at its C-terminus of a peptide linker that forms a random coil. The linker is used to attach a targeting ligand. See abstract.

The linker is designed to accomplish three goals:

(a) serving as a site for the introduction of multiple peptide coding sequences;

(b) presenting the new peptide coding sequences so as to avoid steric hindrance from the structural fiber protein at the knob portion of the fiber protein; and

(c) not interfering with the normal trimerization of the protein.

These goals were accomplished by designing a nucleotide sequence coding for a random coil peptide that would permit any ligand to extend beyond the end of the fiber

trimer complex. See column 4, lines 35-48. Curiel exemplifies as a linker SEQ ID NO:1, which comprises instant SEQ ID NO: 25. See column 6, lines 18-25, and claim 3. SEQ ID NO:1 of Curiel differs from instant SEQ ID NO:25 by the inclusion of a C-terminal S residue. Instant claim 4 is interpreted as embracing this embodiment as it is drawn to a linker "having the sequence" of SEQ ID NO: 25. Note also that the instant specification teaches that the linker used to construct a fiber protein comprising MSH beta included this C-terminal serine and so was identical to the linker used by Curiel.

The vectors of Curiel may contain genes encoding herpes simplex virus thymidine kinase (HSV TK) or other therapeutic proteins. See e.g. paragraph bridging columns 9 and 9, and column 9, lies 27-37. HSV TK is considered to be a cell growth inhibiting factor inasmuch as it can cause cell death.

Curiel does not teach the use of MSH as a targeting ligand, the use of genes encoding cytosine deaminase, a tumor suppressor, or a cell cycle regulator, as an exogenous gene. Curiel is silent as to whether the adenoviruses may contain E1A or E1B.

Spooner teaches the use of MSH alpha as a targeting ligand for adenoviral vectors. See abstract; page 4, lines 24-27; page 6, lines 10-15; page 9, lines 11 and 12; page 10, lines 13-15; page 32, lines 1 and 2, and claims 3, 9-11, 2, and 23. Pertinent to claims 9-14, the viral vector may comprise a gene encoding a molecule having direct or indirect cytotoxic function such as ricin, TNF, cytosine deaminase or herpes simplex virus thymidine kinase, or encoding a tumor suppressor or cell cycle/cell death regulator such as p53, Rb, src, or bcl. See page 16, lines 7-27, and page 20,

lines 27 and 28. Regarding claim 15, Spooner teaches viruses comprising an E1A gene, and/or fragments of an E1B gene. See page 14, lines 20-25. Although these genes are not exogenous to the virus, they are considered to meet the limitations of claim 15 because they are structurally indistinguishable from exogenous versions of the same genes that would be inserted into a virus.

Before discussing the combination of the references to render the invention obvious, the likelihood of success of producing the claimed virus will be considered. It is noted that at page 8, lines 4-16 of the instant specification, Applicant asserts that obtaining useful viruses comprising targeting ligands integrated into a viral coat protein is completely unpredictable until the virus is reduced to practice and shown to be infective. Applicant relies for support on Wickham et al (J. Virol. 71(11): 8221-8229, 1997), who constructed several modified adenoviral fiber proteins by incorporating different targeting ligands into the fiber proteins. Wickham found that:

1) two modified fiber proteins did not allow recovery of viral particles,

2) two modified fiber proteins that did allow recovery of viruses did not support infection of target cells at a rate greater than unmodified adenovirus, and

3) on the other hand, several of the modified fiber proteins supported recovery of viruses that allowed improved and specific infection of target cells. See e.g. Table 1 at page 8223, paragraph bridging columns 1 and 2 on page 8224, last paragraph of column 1 on page 8225, and first two paragraphs of column 2 on page 8225.

Wickham indicates that the failure of two fiber proteins to support virus recovery suggests that the targeting ligands were incompatible with the correct folding of the fiber

protein. See sentence bridging columns 1 and 2 on page 8224. However, Curiel addresses this problem explicitly in requiring that the targeting ligand must be attached to the C-terminus of the fiber protein by a linker that forms a random coil so as to not interfere with normal trimerization of fiber protein. See abstract, and column 4, lines 35-47. To that end, Curiel exemplifies a linker comprising instant SEQ ID NO:25, i.e. PASASASASPGS. Thus Curiel provides a means to overcome the fiber protein folding problem encountered by Wickham.

In addressing the failure of some assembled viruses to provide specific binding, Wickham proposed that the ligands used in these cases were of insufficient affinity to their targets to increase the level of adenovirus binding relative to unmodified virus. For example, Wickham compared two RGD motif-containing ligands, one comprising a single high affinity RGD motif, and one comprising three lower affinity RGD motifs. The triple RGD motif ligand did not provide any increase in binding and infection above wild type, whereas the single high affinity RGD motif did provide increased binding. And infection. Wickham notes that the high affinity RGD motif has a 100-fold higher affinity for target than other RGD motifs. The triple RGD motif does not have this high affinity sequence. See Table 1 at page 8223, and first full paragraph of column 1 at page 8228. Thus the difference in binding and infection is readily explained by the affinity of the ligand for the target. Furthermore Curiel addresses this issue by requiring that the linker must be designed to avoid steric hindrance of binding of the fiber protein to a targeted cell, and proposes that this can be achieved through the use of a random coil-forming linker such as SEQ ID NO:1, i.e. PASASASASPGS. As such the prior art

addresses the concerns of Applicant regarding the unpredictability modified fiber proteins. If one selects a ligand with sufficiently high receptor, and follows the teachings of Curiel in constructing the moc one has a reasonable expectation of making a virus that specifically receptor. All that remains to render the invention obvious is the nec combine the teachings of the prior art.

It would have been obvious to one of ordinary skill in the art at invention to use the MSH alpha targeting ligand of Spooner in the inv One would have been motivated to do so because Curiel teaches that binds to a cell surface receptor my be used (column 6, lines 63-66), a Spooner suggests targeting adenoviral vectors to melanocyte stimulati receptors through the modification of the fiber protein with an MSH alp would have been similarly obvious to include an exogenous gene encoc deaminase, a tumor suppressor, or a cell cycle regulator, because Curi any gene appropriate for therapy may be included in the vector (see e.g. es 58-65), and because Spooner suggests the use of genes such p53, Rb, which are tumor suppressors that help in controlling the cell cycle, and in stic growth. It is noted that p53 also regulates apoptosis and is therefore a ce regulator. It would also be obvious to include an E1A or E1B gene in the s because Curiel does not teach that these genes should be removed from t. As such it would be obvious to leave the endogenous copies in the vectors. Tting adenoviruses would render obvious the claims because they would be stru

indistinguishable from adenoviruses to which an exogenous E1A or E1B had been added. Furthermore, Spooner suggests the inclusion of E1A for its activity as an inducer of apoptosis. See page 14, lines 20-25.

Thus the invention as a whole was *prima facie* obvious.

Claims 1 and 6 are rejected as unpatentable Curiel et al (US Patent 6,312,699, issued 11/6/01) in view of Spooner et al (WO 94/10323, published 5/11/94), Wickham et al (J. Virol. 71(11): 8221-8229, 1997), and Scherz et al (US Patent 5,650,292, issued 7/22/97).

The teachings of Curiel, Spooner, and Wickland are summarized above and can be combined to render obvious adenoviral vectors comprising a fiber protein comprising an MSH alpha peptide wherein the virus specifically binds to a melanocyte-stimulating hormone receptor.

These references do not teach the use of MSH beta or MSH gamma as ligands.

Scherz teaches that alpha, beta, and gamma MSHs specifically bind to melanocyte stimulating hormone receptors and may be substituted for one another as targeting ligands. See column 3, lines 44-53.

MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). Because Scherz teaches that alpha, beta, and gamma MSHs each can act as a targeting ligand via the melanocyte stimulating hormone receptor, there are considered to be art recognized equivalents for the purpose of targeting, and it would have been obvious to substitute one for the other in the instant invention.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441 until 1/13/04, and thereafter will be 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at 703-306-3217 before 2/22/04, and at 571-272-0811 after 2/22/04. The official central fax number is 703-872-9306 until further notice. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413 prior to 1/14/04, and thereafter will be 571-272-0564.

DAVID T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.